Pharmacokinetics of ND0612 administered at different infusion sites and with different cannula lengths: An open-label, randomized, cross-over study in healthy volunteers

Tal Birnberg[1], Cecile Durlach[1], Tami Yardeni[1], Shir Orenbach[1], Sheila Oren[1], Liat Adar[1]

[1]*NeuroDerm Ltd., Rehovot, Israel*

Background

- Continuous levodopa/carbidopa (LD/CD) infusion is considered an appropriate delivery route for treating patients with Parkinson's disease (PD) and motor fluctuations because it has been shown to avoid the peaks and troughs associated with oral dosing.[1]
- Due to poor levodopa solubility, current infusion systems must be surgically routed to the duodenum and are associated with potentially serious complications.[2]
- ND0612 is a drug-device combination designed to provide continuous delivery of LD/CD subcutaneous (sc) solution for patients with PD experiencing motor complications.
- Two previous phase 2 trials have demonstrated that ND0612 maintained steady, therapeutic levodopa plasma concentrations that were associated with reduced OFF time.[3,4]

Objective

Prior studies have primarily used the abdomen as the main infusion site. The aim of this study was to evaluate the impact of sc infusion site location (outer thigh and back vs. the abdomen) and cannula length (short [6 mm] vs. long length [10 mm]) on levodopa pharmacokinetics administered as a single 16-hour sc infusion of ND0612 in healthy volunteers.

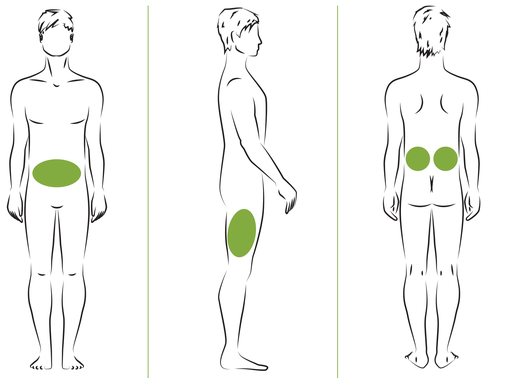
Conclusions

- This Phase 1 study shows that in healthy volunteers both the rate and extent of absorption of ND0612 were similar when administered using different injection site locations and cannula lengths.
- Rotation of infusion sites on a daily basis, including the back and outer thighs, may help patients tolerate local infusion site reactions.

Methods

- This study was a single center, open-label, randomized, single-dose, 4-period, crossover study in 24 healthy volunteers (16 male and 8 female).
- Volunteers were randomized 1:1:1:1 into one of four sequences. Each volunteer sequentially received ND0612 (LD/CD 60/7.5 mg/mL) at three different infusion sites, with the abdomen infused twice, once with a long cannula (the reference route of administration) and once with a short cannula. The outer thigh and back sites were assessed with long cannula. Each of the 4 individual 16-hour dosing periods were separated by a 32-hour washout period.

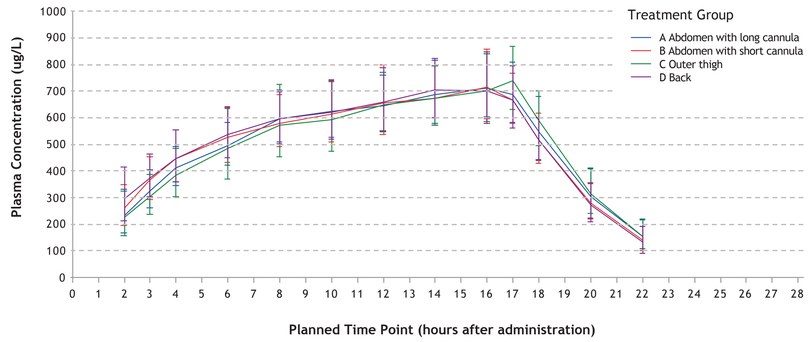
Infusion approaches tested



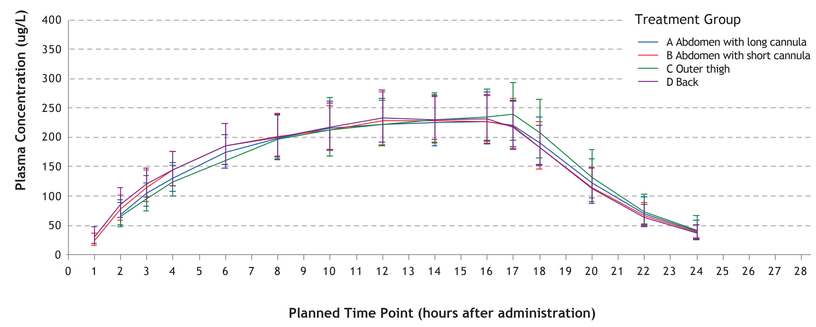
Abdomen (Short and Long Cannula) | Outer thigh (Long Cannula) | Back (Long Cannula)

Results

Levodopa plasma profiles were similar in the different treatment groups, confirming equivalence



Carbidopa plasma profiles were similar with treatment groups, confirming equivalence



PK parameters confirmed bioequivalence of test groups vs reference

Parameter	Statistics	Abdomen with long cannula (reference) (N=24)	Abdomen with short cannula (N=24)	Outer thigh with long cannula (N=23)*	Back with long cannula (N=24)
C_{max}	Geometric mean (ng/mL)	744.9	741.2	787.2	768.7
	Means ratio		99.51	106.92	103.20
	CI (90%)		95.72, 103.45	102.84, 111.17	99.59, 106.94
$AUC_{(0-24)}$	Geometric mean (ng/mL)	10940	10920	10770	11090
	Means ratio		99.77	99.45	101.31
	CI (90%)		97.39, 102.20	97.50, 101.45	99.30, 103.36
$AUC_{(0-t)}$	Geometric mean (ng/mL)	10980	10890	10760	11050
	Means ratio		99.17	98.90	100.61
	CI (90%)		96.89, 101.50	96.87, 100.97	98.65, 102.61
$AUC_{(0-inf)}$	Geometric mean (ng/mL)	11240	11130	10930	11w320
	Means ratio		99.07	98.70	100.71
	CI (90%)		96.71, 101.49	96.50, 100.96	98.65, 102.81

**One volunteer had an unscheduled pump interruption*

90% confidence intervals for all PK parameters were within the pre-defined limits of 80-125% between all tests and the reference, indicating bioequivalence.

Treatment emergent adverse events

	Abdomen long cannula (N=24)	Abdomen short cannula (N=24)	Outer thigh long cannula (N=24)	Back long cannula (N=24)	Overall (N=24)
Infusion site reactions	12 (50.0)	17 (70.8)	12 (50.0)	5 (20.8)	21 (87.5)
Nodule	12 (50.0)	16 (66.7)	11 (45.3)	3 (12.5)	20 (83.3)
Pain	2 (8.3)	0	5 (20.8)	1 (4.2)	6 (25.0)
Irritation	0	1 (4.2)	0	0	1 (4.2)
Warmth	0	0	0	1 (4.2)	1 (4.2)
Eschar	0	2 (8.3)	0	0	2 (8.3)

References

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2. Olanow CW, et al. Lancet Neurol 2014;13(2):141-149.
3. Giladi N, et al. *Mov* Disord. 2017; 32 (suppl 2).
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Disclosures

Cecile Durlach, Tal Birnberg, Tami Yardeni, Sheila Oren and Liat Adar are employed by NeuroDerm

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